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Prognostic markers for the development of type 1 diabetes in first-degree relatives of diabetic patients

Markery ryzyka rozwoju cukrzycy typu 1 u krewnych I stopnia osób chorych na cukrzycę typu 1

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Abstract

Introduction: The aim of this study was to evaluate beta-cell function and insulin resistance in relation to the occurrence of anti-islet antibodies in first degree relatives of patients with type 1 diabetes (T1D).

Material and methods: The group studied consisted of 90 relatives and 60 healthy individuals without a family history of diabetes. An intravenous glucose tolerance test (IVGTT) was performed in all participants and the first phase insulin response index (FPIR) was calculated. Serum concentrations of GADA, IAA and IA-2A were measured by RIA. HOMA-IR and HOMA%B indices were calculated using a computer calculator from website.

Results: At least one positive antibody was found in 28 relatives (31.1%) but in none of the controls. The most frequently detected antibodies were IAA (22.2%). The relatives of diabetic patients had significantly higher fasting insulin level (p), significantly lower FPIR index (p), as well as higher HOMA-IR (p) and lower HOMA%B (p) compared to the controls. A positive correlation between IAA concentration and HOMA-IR ($r = 0.287$, $p < 0.005$) and a negative correlation between IAA level and HOMA%B ($r = –0.226$, $p < 0.05$) were also shown.

Conclusions: Our results confirmed that more than 30% of the first-degree relatives of diabetic patients have positive markers of autoimmune beta-cell destruction. The study showed also that these individuals, in spite of normal glucose tolerance, have markedly decreased beta-cell secretory reserve and decreased sensitivity to insulin action, strongly suggesting an increased risk for developing diabetes later in life. **(Endokrynol Pol 2014; 65 (3): 176–180)**

Key words: *type 1 diabetes; autoantibodies; first-phase insulin secretion; HOMA-IR; HOMA%B*

Streszczenie

Wstęp: Celem pracy była ocena funkcji komórek beta i wrażliwości na insulinę w zależności od obecności przeciwciał skierowanych przeciwko antygenom wysp trzustkowych, u krewnych I stopnia osób chorych na cukrzycę typu 1 (T1D)

Materiał i metody: Grupę badaną stanowiło 90 krewnych I stopnia oraz 60 osób z ujemnym wywiadem rodzinnym w kierunku cukrzycy (grupa kontrolna). U wszystkich badanych dokonano pomiaru przeciwciał GADA, IAA i IA-2A (RIA), a następnie wykonano dożylny test tolerancji glukozy z oceną pierwszej fazy wydzielania insuliny oraz obliczono wskaźniki HOMA-IR i HOMA%B.

Wyniki: Podwyższone stężenie przynajmniej jednego przeciwciała stwierdzono u 28 krewnych (31,1%), przy czym najwyższy odsetek dotyczył przeciwciał IAA (22,2%). Obecności przeciwciał przeciwwyspowych nie obserwowano w grupie kontrolnej. W grupie krewnych wykazano ponadto istotnie wyższe stężenie insuliny na czczo ($p < 0,005$), istotnie obniżony wskaźnik pierwszej fazy wydzielania insuliny ($p < 0,005$), jak również znamiennie wyższy wskaźnik HOMA-IR ($p < 0,005$) i niższy wskaźnik HOMA%B ($p < 0,05$) w porównaniu z grupą kontrolną. Stwierdzono także dodatnią korelację pomiędzy stężeniem IAA i HOMA-IR ($r = 0,287$, $p < 0,005$) oraz ujemną pomiędzy stężeniem IAA i HOMA%B ($r = –0,226$, $p < 0,05$).

Wnioski: Wyniki potwierdzają obecność markerów autoimmunologicznej destrukcji komórek beta u ponad jednej trzeciej krewnych pacjentów z cukrzycą typu 1. Krewni I stopnia, pomimo prawidłowej tolerancji glukozy, charakteryzują się zaburzeniami pierwszej fazy wydzielania insuliny oraz zmniejszoną wrażliwością na insulinę, co może wskazywać na podwyższone ryzyko rozwoju cukrzycy typu 1 w przyszłości. **(Endokrynol Pol 2014; 65 (3): 176–180)**

Słowa kluczowe: *cukrzyca typu 1; przeciwciała przeciwwyspowe; pierwsza faza wydzielania insuliny; HOMA-IR; HOMA%B*

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Introduction

Type 1 diabetes occurs when autoimmune destruction of beta cells reaches a stage at which metabolic stability is no longer maintained. To date, it is not well understood when this autoimmune destruction begins in relation to the clinical presentation of the disease and what screening tests can accurately select the subjects who are at risk for developing the disease [1]. Moreover, it has been suggested that not

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only decreased beta-cell secretory reserve but also decreased sensitivity to insulin action may impact upon the progression of the autoimmune process and promote the development of hyperglycaemia in subjects with autoantibodies directed against pancreatic islet antigens [2]. The assessment of first phase insulin secretion together with the measurement of antibodies against pancreatic antigens are regarded as the most sensitive prognostic indicators of the risk for the development of type 1 diabetes, especially in genetically predisposed persons and high risk groups, such as first degree relatives of patients [3]. The presence of circulating autoantibodies to glutamic acid decarboxylase (GADA), insulin autoantibodies (IAA) and autoantibodies to thyrosine phosphatase (IA-2A), as well as the antibodies that recognise the zinc transporter autoantigen (ZnT8) identifies underlying islet autoimmune pathology and an increased risk of diabetes. This risk has been shown to be related to both the number and the levels of islet antibodies, as well as to the degree of impaired insulin secretion [5]. Moreover, some data shows that the presence of GADA and IA-2A in combination has a high specificity and sensitivity for the prediction of future clinical onset of the disease. IAA are usually the first antibodies that appear in the relatives of diabetic patients, especially in young children [6–8]. The role of anti-islet antibodies and a decline in first-phase insulin response (FPIR) in predicting type 1 diabetes has been confirmed by the results of The Diabetes Prevention Trial — Type 1 (DPT-1) [9] but the contribution of impaired insulin sensitivity and action to the development of type 1 diabetes has received little attention so far.

The aim of the present study was to evaluate the first phase insulin secretion, as well as insulin resistance measured by HOMA-IR in relation to the presence of antibodies against pancreatic islets in first degree relatives of patients with type 1 diabetes, and healthy individuals without a family history of diabetes.

Material and methods

The group studied consisted of 90 first-degree relatives (parents, siblings and offspring) of patients with type 1 diabetes (48 women and 42 men, mean age 34.4 ± 15.7 [18–67] years and mean BMI 22.4 ± 4.6 [15.5-38] kg/m^2) and 60 healthy individuals (36 women and 24 men, mean age 32.9 ± 13.7 [18–60] years and mean BMI 22.8 ± 2.3 [18–26.3] kg/m^2) with no family history of diabetes or other autoimmunological disorders.

All subjects underwent a 75 g oral glucose tolerance test (OGTT) and persons with an abnormal result or/and the presence of an autoimmune disease were not included. Written informed consent was obtained from all participants, and the protocol was approved by the local ethics committee (Medical University of Bialystok).

To evaluate the first phase insulin secretion, an intravenous glucose tolerance test (IVGTT) was performed 5–7 days after the OGTT by intravenous administration of 25% glucose solution in a dose of 0.5 g/kg of body weight (up to 35g) for 3 min (± 15 s). Serum insulin levels were measured at 0, 1, 3 and 5 min. by immunoenzymatic method (BioSource Europe, S.A., Belgium). The first phase insulin response index (FPIR) was calculated as the sum of the serum insulin concentrations at 1 and 3 min after intravenous glucose administration [5]. Plasma glucose concentrations were measured using oxidase method (CORMAY, Poland). HOMA%B (Homeostatic Model Assessment of β Cell Function) and HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) were calculated using a computer calculator located at www.OCDEM.ox.ac.uk (Oxford Centre for Diabetes, Endocrinology and Metabolism). Glutamic acid decarboxylase antibodies (GADA), insulin autoantibodies (IAA) and protein tyrosine phosphatase-2 antibodies (IA-2A) were determined by commercial radioimmunoassays (CIS Bio International, France). Cut-off values for each antibody positivity were calculated as the 99th percentile of antibody level in 350 nondiabetic persons and were as follows: 1.0 U/mL for GADA, 9.8 U/mL for IAA and 0.75 U/mL for IA-2A.

Statistical analysis was performed using STATISTICA 8.0 software (Statsoft, Tulsa, OK, USA). Before analysis, data was tested for normality of distribution using the Shapiro-Wilk test. Differences between the groups were compared by Mann Whitney U test and relationships between variables were tested by Pearson's correlations after log-transformation of non normally distributed variables. P value of less than 0.05 was regarded as statistically significant.

Results

Clinical characteristics of the groups studied

The clinical and biochemical characteristics of the groups studied are summarised in Table I. There were no significant differences in mean BMI and fasting glucose values between the group of relatives and the controls. The relatives of diabetic patients had statistically significantly higher levels of GADA and IAA ($p < 0.05$ and $p < 0.0001$, respectively), higher HOMA-IR ($p < 0.05$), as well as lower HOMA%B ($p < 0.05$) and FPIR index ($p < 0.05$) than had the controls (Table I).

At least one positive antibody was found in 28 relatives (31.1%) and in none of the controls. IAA was detected in 17 persons (18.9%), GADA in seven (7.8%)

Table I. *Clinical characteristics of the groups studied*
Tabela I. *Charakterystyka kliniczna badanych grup*

	Study group n = 90 mean ± SD med. (min.–max.)	Control group n = 60 mean ± SD med. (min.–max.)	p
BMI [kg/m²]	22.1 ± 4.9	22.8 ± 2.3	p = 0.7
	21.4 (16–38)	22.8 (18–26)	
Fasting glucose [mg/dL]	86.7 ± 7.3	84.8 ± 5.2	p = 0.2
	87.0 (82–91)	85.5 (80–89)	
GADA [U/mL]	6.0 ± 28.7	0.7 ± 0.1	p < 0.05
	0.8 (0.6–218.7)	0.7 (0.6–0.9)	
IAA [U/mL]	6.9 ± 1.4	4.4 ± 0.8	p < 0.01
	6.8 (4.4–13.2)	4.5 (3.1–5.6)	
IA-2A [U/mL]	0.6 ± 0.7	0.6 ± 0.1	p = 0.7
	0.6 (0.6–0.9)	0.6 (0.6–0.7)	
HOMA%B	92.8 ± 29.4	114.0 ± 47.1	p < 0.01
	84.2 (64.4–180.0)	99.5 (37.3–231.8)	
HOMAIR	1.2 ± 0.6	0.8 ± 0.3	p < 0.001
	1.0 (0.3–3.0)	0.7 (0.5–1.9)	
FPIR	91.9 ± 62.9	124.1 ± 55.4	p < 0.005
	78.7 (49.4–128.7)	108.3 (80.6–171.0)	

and IA-2A in one subject (1.1%). The presence of two antibodies (IAA and GADA) was found in two persons and the coexistence of all three antibodies was noted in one person.

In the group of relatives, there was a positive correlation between BMI and HOMA-IR (r = 0.19, p < 0.05), but no significant correlations between BMI and immunological markers were noted in both groups studied.

First phase insulin response and islet autoimmunity

The relatives of diabetic patients had statistically significantly higher fasting insulin concentration (7.7 μIU/mL ± 4.3 *vs.* 5.3 μIU/mL ± 2.3 p < 0.005) and statistically significantly lower insulin levels at the 1st and 3rd mins of the IVGTT (46.2 μIU/mL ± 33.5 *vs.* 64.3 μIU/mL ± 34.1, p < 0.01 and 45.9 μIU/mL ± 30.7 *vs.* 59.7 μIU/mL ± 24.9, p < 0.005, respectively) than had the controls (Fig. 1). Insulin concentration at the 5th min of the test was also lower in the study group than in the controls, but the difference was not significant (41.9 μIU/mL ± 29.3 *vs.* 47.9 μIU/mL ± 22.9, p = 0.05). Statistically significantly higher fasting insulin concentrations were also observed in the group of relatives with positive IAA compared to the subjects without these antibodies (9.4 μIU/mL ± 4.3 *vs.* 7.3 μIU/mL ± 4.2; p < 0.05). In the same group, mean insulin concentrations at the 1st, 3rd, and 5th mins of the IVGTT were lower than in the subjects with negative antibodies but the differences were not statistically significant.

The percentage of subjects with positive antibodies was similar in the subgroup with very low (< 25th quartile), low (between 25th and 50th quartile) and medium (50th–75th quartile) FPIR index (30.3%) and insignificantly lower than in the subgroup with the highest (> 75th quartile) FPIR index (33.3%). In the group of relatives, FPIR index correlated positively with HOMA%B (r = 0.59, p = 0.0001) and negatively with fasting plasma glucose concentration (r = –0.24, p = 0.03), but not with the levels of IAA or GADA.

HOMA indices and islet autoimmunity

HOMA%B index below 100% was found in 41 relatives, among whom there were seven persons with the index below 50%. A negative correlation between IAA and HOMA%B (r = –0.23, p < 0.05) was observed in the study group. HOMA-IR index above 1 was found in 37 relatives, and 11 of them had the index above 2. In the group of relatives, HOMA-IR correlated positively with IAA concentration (r = 0.29, p < 0.005; Fig. 1) but not with other antibodies levels.

Discussion

The constant increase in the incidence of type 1 diabetes, observed worldwide, has aroused interest in accu-

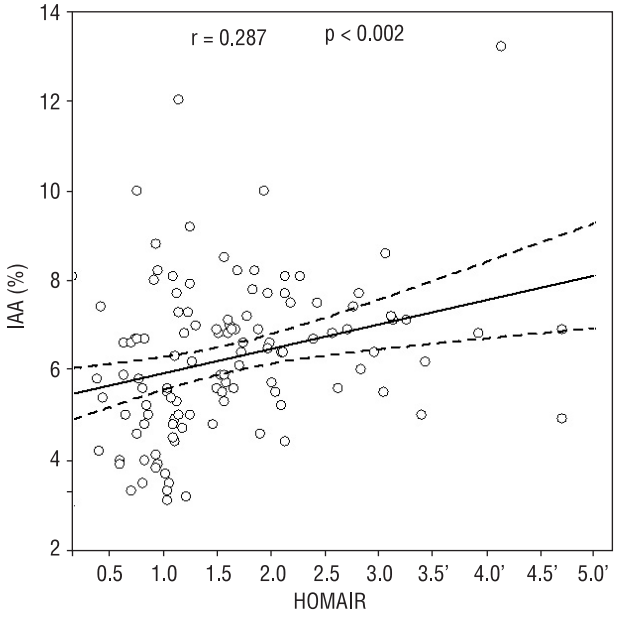

Figure 1. *Correlation between IAA and HOMA-IR in the study group*

Rycina 1. *Korelacja pomiędzy IAA i HOMA-IR w grupie badanej*

rate and reliable predictors of the future development of the disease. The data from DPT-1 [9] and other trials carried out on first degree relatives of patients with type 1 diabetes [5–8] has confirmed the prognostic value of immunological markers such as GADA, IAA and IA-2A. It has been also demonstrated that the possibility of identifying persons who would develop diabetes later in life increases with the number and mean concentration(s) of anti-islet antibodies [10–12]. Moreover, a large analysis based on the DPT-1 data [9] showed that in first degree relatives of patients with type 1 diabetes, the destruction of pancreatic beta cells is accompanied by impaired first phase insulin secretion, identifying the IVGTT-derived indices, such as FPIR, as having a significant predictive accuracy for selecting individuals likely to progress to the clinical onset of type 1 diabetes within the next five years.

The present study revealed that the relatives of diabetic patients had statistically significantly higher levels of GADA and IAA, as well as lower HOMA%B and FPIR indices, than had persons with no family history of diabetes. Moreover, at least one positive antibody was found in 31.1% of the relatives and in none of the controls. It is also worth noting that nearly 19% of the relatives had elevated levels of IAA which are regarded as having the best predictive value. Therefore, it might be hypothesised that these individuals are at substantial risk of developing type 1 diabetes later in life. Furthermore, a negative correlation between IAA and HOMA%B observed in the study group seems to confirm the impact of the autoimmune process on decreased beta-cell secretory reserve, although no significant association between the incidence or/and the levels of anti-islet antibodies and the first phase insulin response was shown in our study. It should be mentioned that in the previous studies an impairment of the first phase insulin secretion was more pronounced in individuals with the presence of islet autoantibodies [13] and that high titres of GADA and IAA were negatively associated with the early phase insulin secretion indices [14–16]. It is also noteworthy that despite lower insulin levels during the IVGTT, the relatives of diabetic patients — especially these with positive autoantibodies — had significantly higher fasting insulin concentrations and higher HOMA-IR index than had the controls. Moreover, a positive correlation between IAA levels and HOMA-IR was found in the study group, confirming the previous observations suggesting that not only decreased beta-cell secretory reserve, but also increased insulin resistance, impact upon the progression of the autoimmune process, especially in subjects with auto-antibodies directed against pancreatic islet antigens [17–19]. Abnormal sensitivity to insulin in patients with type 1 diabetes was shown for the first time by Ginsberg in the 1970s [20]. Moreover, the recently published Wilkin's 'accelerator hypothesis' suggests that type 1 and type 2 diabetes are parts of the same disease, with two key accelerators of β-cell loss: autoimmune destruction and insulin resistance [21]. However, the possible influence of insulin resistance on the progression of type 1 diabetes seems still controversial. Ma et al. [22] in a large study carried out on first degree relatives of patients with type 1 diabetes observed that the presence of autoantibodies had no impact on insulin sensitivity, although the disposition index, which is a measure of beta-cell response to a given insulin sensitivity level, was markedly lower in the relatives with positive autoantibodies. Other authors, however, have reported that first-degree relatives positive for islet antibodies and with insulin resistance progressed most rapidly to diabetes, suggesting that better insulin sensitivity might delay development of the disease [23–25].

Conclusions

In conclusion, although there is no gold standard in predicting the future development of type 1 diabetes, our results confirmed that more than 30% of the first-degree relatives of diabetic patients have positive markers of autoimmune beta-cell destruction. Furthermore, the present study showed that these individuals, in spite

of normal glucose tolerance, have markedly decreased beta-cell secretory reserve and decreased sensitivity to insulin action, strongly suggesting an increased risk for developing the disease later in life.

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